UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

TXR Number: 1003246

MEMORANDUM

DATE: April 4, 2012

SUBJECT: ***Terbutryn:*** Evaluation of the Rat Combined Chronic Toxicity/Carcinogenicity Study – "Fankhauser, H. (2001) 24-Month carcinogenicity and chronic toxicity study in rats. Syngenta Crop Protection AG, Stein, Switzerland. Laboratory Study No.: 951040, May 8, 2001. MRID 48348901. Unpublished."

PC Code: 080813	DP Barcode/No.: D386095
Decision No./Submission No.: 417489	EPA Registration Number: 5383-RGI
Petition No(s).: N/A	Regulatory Action: Data Evaluation Record (DER), Toxicology Review for Product Registration
Risk Assess Type: Single Chemical	Case No.: N/A
TXR No.: 1003246	CASRN(s): N/A
MRID No(s).: 47213001	40 CFR: None

FROM: Jonathan Chen, Ph.D.
Risk Assessment and Science Support Branch (RASSB)
Antimicrobials Division (7510P)

THRU: Tim F. McMahon, Ph.D., Division Senior Toxicologist
Immediate Office
Antimicrobials Division (7510P)

Nader Elkassabany, Ph.D., Branch Chief
Risk Assessment and Science Support Branch (RASSB)
Antimicrobials Division (7510P)

TO: Stacy Grigsby, Risk Manager Reviewer
Regulatory Management Branch II
Antimicrobials Division (7510P)

Action Requested: Review the toxicity study submitted by the Troy Chemical Corp.

Fankhauser, H. (2001) 24-Month carcinogenicity and chronic toxicity study in rats. Syngenta Crop Protection AG, Stein, Switzerland. Laboratory Study No.: 951040, May 8, 2001. MRID 48348901. Unpublished.

Agency Conclusion: In a combined chronic toxicity/carcinogenicity study (MRID 48348901), Sprague-Dawley-derived (Tif: RAIf) rats (70/sex/dose) were exposed to terbutryn (97.2-97.7% a.i.; Batch No.: P. 506001) in the diet at concentrations of 0, 30, 100, 300, or 600 ppm (equivalent to 0/0, 1.19/1.40, 4.03/4.69, 12.0/14.0, and 24.8/29.8 mg/kg bw/day [M/F]) for up to 2 years. Animals were subdivided into three groups: carcinogenicity group (n=50), hematology (n=10), and a group for hematological, biochemical, and urine analysis (n=10). Additionally, 10 rats/sex/dose were treated at the same doses for up to 1 year and then sacrificed.

No treatment-related effects were observed on mortality, clinical signs, water consumption, ophthalmoscopic examinations, hematology, clinical chemistry, urinalysis, or organ weights.

Body weights were decreased ($p<=0.05$) throughout treatment at 600 ppm by 4-12% in males and by 4-21% in females. During the first 14 weeks of treatment, body weight gains decreased by 8% in males and by 18% in females. Overall body weight gain (weeks 1-103) was decreased ($p<=0.05$) by 15% in males and 29% in females. Food consumption was slightly decreased throughout the study, frequently attaining statistical significance, resulting in cumulative (weeks 1-103) decreased food consumption (g/animal) of 5% in the males and 9% in the females. Additionally, food consumption ratios (g food consumed/kg body weight/day) were increased from week 22 (males) or 38 (females) throughout the remainder of the study, indicating food efficiency was impacted at this dose level. Maximum deviations from controls of 12% (males) and 16% (females) were obtained at Week 83.

At 600ppm, after 2 years, treatment-related increased ($p\leq0.05$; except as noted) incidences were noted: (% affected in treated [severity] vs controls [severity]; (i) lung foam cells in the males (68% [minimal to massive] vs 44% [minimal to massive]); (ii) thyroid gland follicular cell hypertrophy in males (60% [minimal to slight] vs 34% [minimal to slight]); (iii) thyroid gland follicular cell hyperplasia in males (10% [moderate to marked] vs 2% [massive]); (iv) spleen hemosiderosis in females (54% [minimal to marked] vs 28% [minimal to moderate]); (v) uterus hyperplastic glandular cyst (16% [minimal to marked] vs 10% [minimal to moderate]; NS); and (vi) uterus stromal polyp (12% [moderate to marked] vs 2% [moderate]). All these are considered treatment-related effects.

The LOAEL is 600 ppm (equivalent to 24.8/29.8 mg/kg/day in males/females), based on decreased body weights, body weight gains, food consumption and microscopic lesions in both sexes. The NOAEL is 300 ppm (equivalent to 12.0/14.0 mg/kg/day in males/females).

After 2 years at 600 ppm in male rats, the incidence of pancreatic acinar adenoma was increased: one tumor (47% treated vs 21% controls; $p\leq0.05$), two tumors (20% treated vs 2% controls), and

more than two tumors (8% treated vs. 0%). Dosing was considered adequate based on decreased body weights and body weight gains. Because (i) the effect did not show a clear dose-dependency manner; (ii) the effect was seen in male rats only; and (iii) the control group has incidence (21%) higher than the historical control incidences (ranging from 2 to 14.29%), reviewer agree the researcher's discussion, the toxicological significance of the increased pancreatic acinar adenoma is questionable.

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OCSPP 870.4300; OECD 453) for a combined chronic toxicity/carcinogenicity study in rats.

There are two previous cancer studies:

Mouse two year cancer/chronic study (MRID 00029135):

A two year carcinogenicity study in Charles River CD-1 mice (MRID # 00029153) is available, in which technical terbutryn was administered in the diet at levels of 0, 3, 1000 and 3000 ppm. The test material was terbutryn technical. No treatment related effects were seen on general behavior, appearance, body weight gain, food consumption or survival. No evidence of oncogenicity was observed for terbutryn in this study.

Rat two-year cancer/chronic study (MRID 00035923)

In the rat two year cancer/chronic study, CD rats (MRID # 00035923) is available in which the oncogenic potential of technical terbutryn was studies. Levels tested were 0, 2, 300 and 3000 ppm (0, 0.1, 15, and 150 mg/kg/day). At 3000 ppm in the diet terbutryn induced a statistically significant increase in the number of mammary tumor bearing female rats, in combined hepatocellular adenomas and carcinomas in female rats in combined thyroid follicular cell adenomas and carcinomas in male rats and in testicular interstitial cell adenomas in males at the highest dose tested.

On the December 23, 1987, Agency presented the study results of the two previous chronic/cancer studies to the Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP). SAP concluded "tumors were induced at multiple sits only at the highest dose, which exceeded a maximum tolerated dose (MTD). Good dose-response data were not available due to the large spread between doses. Therefore the panel believes that an interim category C is appropriate, but that this could be reduced to a category D if negative data from more appropriate does were submitted. Furthermore, the panel does not believe a quantitative risk assessment (for the carcinogenic effects) is justified since positive tumor Data occurred only at does that exceeded the MTD".

On January 13, 1988, the Office of Pesticide Programs (OPP) Peer review Committee for Terbutryn meet to discuss the carcinogenic concern of terbutryn based on the SAP's recommendation. It concluded "the committee concurred with the SAP decision, but felt that science Terbutryn was classified as interim C and science the dosage levels for the rat study (MRID 00035923) were poorly chosen, that another rat oncogenicity study should be required with particular attention paid to dose selection".

Although incidences of hypertrophy of thyroid follicular cells were noticed in current study, it only happened at highest level tested (600 ppm), and no thyroid follicle cell adenoma was noticed. No mammary tumor, no hepatocellular adenomas and/or carcinomas, and testicular interstitial cell adenomas were noticed in the study. Therefore, based on the current study results will not change Agency's classification on interim group C carcinogen and quantitative risk assessment for the carcinogenetic potential of Terbutryn is not needed.

ATTACHMENT

Data Evaluation Record (DER)

Combined chronic toxicity/carcinogenicity study in rats (dietary)

OPPTS 870.4300 [§83-5]

For

Terbutryn

PC Code: 080813

EPA Reviewer: Jonathan Chen, Ph.D.
RASSB, Antimicrobial Division
EPA Secondary Reviewer: Tim McMahon, Ph.D.
RASSB, Antimicrobial Division

Signature: Jonathan Chen
Date: 03/28/2012
Signature:
Date: 03/29/2012

Template version 02/06

DATA EVALUATION RECORD

STUDY TYPE: Combined chronic toxicity/carcinogenicity study in rats (dietary); OPPTS 870.4300 [§83-5]; OECD 453.

PC CODE: 080813 **DP BARCODE:** D386095

TEST MATERIAL (PURITY): Terbutryn (97.2-97.7% a.i.)

SYNONYMS: GS 14260 tech.; *N*-(1,1-dimethylethyl)-*N'*-ethyl-6-(methylthio)-1,3,5-triazine-2,4-diamine

CITATION: Fankhauser, H. (2001) 24-Month carcinogenicity and chronic toxicity study in rats. Syngenta Crop Protection AG, Stein, Switzerland. Laboratory Study No.: 951040, May 8, 2001. MRID 48348901. Unpublished.

SPONSOR: Syngenta Crop Protection, Human Safety Assessment, Basel, Switzerland.

EXECUTIVE SUMMARY: In a combined chronic toxicity/carcinogenicity study (MRID 48348901), Sprague-Dawley-derived (Tif: RAIf) rats (70/sex/dose) were exposed to terbutryn (97.2-97.7% a.i.; Batch No.: P. 506001) in the diet at concentrations of 0, 30, 100, 300, or 600 ppm (equivalent to 0/0, 1.19/1.40, 4.03/4.69, 12.0/14.0, and 24.8/29.8 mg/kg bw/day [M/F]) for up to 2 years. Animals were subdivided into three groups: carcinogenicity group (n=50), hematology (n=10), and a group for hematological, biochemical, and urine analysis (n=10). Additionally, 10 rats/sex/dose were treated at the same doses for up to 1 year and then sacrificed.

No treatment-related effects were observed on mortality, clinical signs, water consumption, ophthalmoscopic examinations, hematology, clinical chemistry, urinalysis, or organ weights.

Body weights were decreased ($p<=0.05$) throughout treatment at 600 ppm by 4-12% in males and by 4-21% in females. During the first 14 weeks of treatment, body weight gains decreased by 8% in males and by 18% in females. Overall body weight gain (weeks 1-103) was decreased ($p<=0.05$) by 15% in males and 29% in females. Food consumption was slightly decreased throughout the study, frequently attaining statistical significance, resulting in cumulative (weeks 1-103) decreased food consumption (g/animal) of 5% in the males and 9% in the females. Additionally, food consumption ratios (g food consumed/kg body weight/day) were increased from week 22 (males) or 38 (females) throughout the remainder of the study, indicating food efficiency was impacted at this dose level. Maximum deviations from controls of 12% (males) and 16% (females) were obtained at Week 83.

At 600ppm, after 2 years, treatment-related increased ($p \leq 0.05$; except as noted) incidences were noted: (% affected in treated [severity] vs controls [severity]; (i) lung foam cells in the males (68% [minimal to massive] vs 44% [minimal to massive]); (ii) thyroid gland follicular cell hypertrophy in males (60% [minimal to slight] vs 34% [minimal to slight]); (iii) thyroid gland follicular cell hyperplasia in males (10% [moderate to marked] vs 2% [massive]); (iv) spleen hemosiderosis in females (54% [minimal to marked] vs 28% [minimal to moderate]); (v) uterus hyperplastic glandular cyst (16% [minimal to marked] vs 10% [minimal to moderate]; NS); and (vi) uterus stromal polyp (12% [moderate to marked] vs 2% [moderate]). All these are considered treatment-related effects.

The LOAEL is 600 ppm (equivalent to 24.8/29.8 mg/kg/day in males/females), based on decreased body weights, body weight gains, food consumption and microscopic lesions in both sexes. The NOAEL is 300 ppm (equivalent to 12.0/14.0 mg/kg/day in males/females).

After 2 years at 600 ppm in male rats, the incidence of pancreatic acinar adenoma was increased: one tumor (47% treated vs 21% controls; $p <= 0.05$), two tumors (20% treated vs 2% controls), and more than two tumors (8% treated vs 0%). Dosing was considered adequate based on decreased body weights and body weight gains.

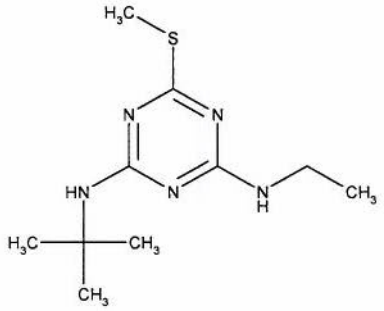
This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OCSPP 870.4300; OECD 453) for a combined chronic toxicity/carcinogenicity study in rats.

COMPLIANCE: Signed and dated GLP Compliance, Quality Assurance, and Data Confidentiality statements were provided. Page 4 in the study report was reserved for a Flagging Statement, which was not provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Terbutryn

Description:	White powder
Batch No.:	P. 506001
Purity (w/w):	97.2-97.7% a.i.
Stability of compound:	The test compound was stable in the dietary formulations for at least 7 weeks at room temperature.
CAS #:	886-50-0
Structure:	

2. Vehicle: Diet

3. Test animals

Species:	Rat
Strain:	Tif: RAIf (SPF), hybrids of RII/1 x RII/2 (Sprague-Dawley derived)
Age and mean group weight at study initiation:	6-7 weeks of age; 220.7-227.7 g males; 166.3-172.6 g females
Source:	CIBA-GEIGY Limited (4332 Stein, Switzerland)
Housing:	5 rats/cage of the same sex were housed in Macrolon type 4 cages
Diet:	Nafag No. 8900 for GLP pelleted, certified standard diet (Provimi Kliba AG Kliba Nafag, Kaiseraugst, Switzerland), *ad libitum*
Water:	Tap water, *ad libitum*, except during urine collection
Environmental conditions	
Temperature:	22±2°C
Humidity:	55±10%
Air changes:	16-20 air changes/hour
Photoperiod:	12 hours light/12 hours dark
Acclimation period:	10 days

B. STUDY DESIGN

1. In life dates: Start: June 12, 1995 End: June 30, 1997

2. Animal assignment: Animals were randomly assigned to the test groups presented in Table 1.

TABLE 1. Study design. [a]			
Nominal Dose (ppm)	Dose to Animal (mg/kg/day; M/F) [b]	Terminal Sacrifice [c] (Week 105; # rats/sex)	Interim Sacrifices [d] (Week 53; # rats/sex)
0	0	70	10
30	1.19/1.40	70	10
100	4.03/4.69	70	10
300	12.0/14.0	70	10
600	24.8/29.8	70	10

a Data were obtained from pages 24 and Table 8.2 on pages 89-90 of the study report.
b Achieved dosages based on the mean measured concentrations in the diet.
c 50 animals/sex/group were designated exclusively for the evaluation of the carcinogenic potential of the test compound and survival analysis. These animals were designated as Group I (or K0) in the study report. 10 animals/sex/group were designated for hematological investigations, and an additional 10 animals/sex/group were designated for hematological, biochemical, and urine analysis. These animals were designated as Groups II and III (or K2) in the study report.
d Animals designated as Group IV (or K1) in the study report.

3. **Dose-selection rationale:** The doses for this study were selected on the basis of a previously conducted subchronic toxicity study in rats and a 2-year chronic oral toxicity study. In the subchronic toxicity study (CIBA-GEIGY Limited Test No. 931124), terbutryn was administered in the diet to rats at dose levels of 0, 30, 1000, or 3000 ppm for 3 months. It was concluded that the maximum tolerated dose was exceeded at 1000 ppm based on decreased body weights. In the chronic toxicity study (International Research and Development Corporation; Revised Report of March 27, 1980), terbutryn was administered in the diet to rats at dose levels of 0, 2, 300, or 3000 ppm for 2 years. At 3000 ppm, female rats exhibited blood chemistry changes, both sexes had significant body weight reductions, and increased incidences of hepatic adenomas were observed in both sexes. No adverse effects were noted at 2 or 300 ppm. So rationale for testing at 600ppm was based on excessive body weight decrease at 1000 ppm and NOAEL of 300 ppm.

4. **Treatment preparation, analysis, and administration:** Dietary formulations were prepared at approximately monthly intervals by mixing a weighed portion of the test substance (unadjusted for purity) with pulverized basal diet. Approximately 25% water was added before pelleting, and the manufactured pellets were air dried and stored in stainless steel containers at room temperature. The concentration of the test compound was measured in samples of dietary formulation at each dose periodically (usually every 1 or 2 months) throughout the treatment period for a total of 13 times. Homogeneity (beginning, middle, and end of pelleting process) of the test material in the diet was measured at each dose. Stability of the test substance in the diet at each dose was determined following storage at room temperature for 5 or 7 weeks. Samples used to measure stability were stored at -18°C prior to evaluation without any appreciable effect on the test compound concentration.

Results

Homogeneity (% coefficient of variation): 1.3-6.2%

Stability (% of Day 0): 96-100% following room temperature storage for 7 weeks

Concentration (% of nominal): 96-109%

The analytical data indicated that the mixing procedure was adequate and that the variation between nominal and actual dosage to the animals was acceptable.

5. **Statistics:** Significant differences were reported at the 5% levels (or exact p-values in some cases). The following statistical analyses were performed.

PARAMETER	STATISTICAL ANALYSES
Body weight Food consumption Water consumption Urinalysis Clinical chemistry Hematology Organ weight data	Lepage test or Wilcoxon's two-sample test (non-parametric tests) Jonckheere's test for ordered alternatives (trend test)
Survival analysis	Cox regression model (partial likelihood)
Pathological findings	Cochran-Armitage's linear trend test stratified by survival differences. The highest non-significant group was determined by deleting the highest dose group and re-performing the analysis until a non-significant result was obtained.
Tumor incidence	Peto's mortality prevalence test. The p-values were computed using exact permutation distributions when marginal success or failure totals within a stratum were 25 or less.

These statistical analyses were considered appropriate.

C. METHODS

1. Observations

a. **Cageside observations:** All animals were observed mornings and afternoons on work days and mornings on weekends and holidays for mortality, and daily for general appearance, behavior, and signs of toxicity.

b. **Clinical examinations:** Detailed physical examinations, which included palpation, were performed weekly.

c. **Neurological evaluations:** Neurological evaluations were not performed.

2. **Body weight:** All rats were weighed prior to treatment, weekly for the first 3 months, monthly thereafter until termination, and at termination. Cumulative body weight gains were reported for the corresponding body weight intervals.

3. **Food consumption, water consumption, and compound intake:** Food consumption (g/rat/week and g/kg bw/day) was reported weekly for each cage for the first 3 months and

monthly thereafter. Water consumption (g/rat/week) was reported monthly for each cage during the first 6 months. Compound intake (mg/kg/day) was calculated from the group mean bodyweight and food consumption data, and overall compound intake was reported uncorrected and corrected for analytically determined content (Table 1).

4. **Ophthalmoscopic examination:** The eyes of all animals designated as the carcinogenicity subgroup (n=50) were examined prior to treatment, and the eyes of animals in the control and 600 ppm carcinogenicity subgroups were examined at 6, 12, 18, and 24 months.

5. **Hematology and clinical chemistry:** Hematology was performed on survivors designated for this purpose (n=20 on Day 1). Clinical chemistry was performed on samples obtained from survivors designated for this purpose (n=10 on Day 1). Samples were collected during Weeks 13, 27, 53, 78, and 105. After overnight fasting, blood was collected from the orbital sinus while the animals were under ether anesthesia. At Week 105, the number of animals designated for hematology was supplemented by animals of the carcinogenicity group to yield 20 samples/sex/group. At Week 105, the animals designated for clinical chemistry was supplemented by animals of the hematology group to yield 10 samples/sex/group. The following CHECKED (X) parameters were examined.

a. Hematology

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpuscular HGB concentration (MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpuscular volume (MCV)*
X	Platelet count*		Reticulocyte count
	Blood clotting measurements*		Cell morphology
	(Activated partial thromboplastin time)	X	Red cell volume distribution width
	(Clotting time)	X	Hemoglobin concentration distribution width
X	(Prothrombin time)		

* Recommended for combined chronic/carcinogenicity studies based on Guideline 870.4300.

b. Clinical chemistry

	ELECTROLYTES		OTHER
X	Calcium	X	Albumin*
X	Chloride	X	Creatinine*
	Magnesium	X	Urea nitrogen*
X	Phosphorus	X	Total cholesterol*
X	Potassium*	X	Globulins
X	Sodium*	X	Glucose*
	ENZYMES (more than 2 hepatic enzymes eg. *)	X	Total bilirubin
X	Alkaline phosphatase (ALP)*	X	Total protein (TP)*
	Cholinesterase (ChE; Plasma and Erythrocyte)	X	Triglycerides
	Creatine phosphokinase	X	A/G ratio
	Lactic acid dehydrogenase (LDH)		Serum protein electrophoresis
X	Alanine aminotransferase (ALT/ SGPT)*		
X	Aspartate aminotransferase (AST/ SGOT)*		
X	Gamma glutamyl transferase (GGT)*		
	Sorbitol dehydrogenase*		
	Glutamate dehydrogenase*		

* Recommended for combined chronic and carcinogenicity studies based on Guideline 870.4300.

6. **Urinalysis:** Urinalysis was performed on samples obtained from survivors designated for this purpose (n=10 on Day 1). Samples were collected during Weeks 13, 27, 53, 78, and 105. At Week 105, the animals designated for urine analysis was supplemented by animals of the hematology group to yield 10 samples/sex/group. Urine was collected overnight while individual animals were housed in metabolism cages without food or water. The following CHECKED (X) parameters were examined.

X	Appearance*	X	Glucose*
X	Volume*	X	Ketones
X	Specific gravity / osmolality*	X	Bilirubin
X	pH*	X	Blood/ red blood cells*
X	Sediment (microscopic)		Nitrate
X	Protein*	X	Urobilinogen

* Recommended for combined chronic and carcinogenicity studies based on Guideline 870.4300.

7. **Sacrifice and pathology:** All animals that died or were sacrificed *in extremis* and those sacrificed on schedule were subjected to gross pathological examination and tissue preservation when possible. Animals were killed by exsanguination under ether anesthesia. The following CHECKED (X) tissues were collected and examined microscopically, except as noted. Additionally, the (XX) organs were weighed (bilateral organs weighed together).

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
X	Tongue	X	Aorta, thoracic*	XX	Brain (multiple sections)*+
X	Salivary glands*	X	Heart*+	X	Peripheral nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	XX	Spleen*+	X	Eyes (retina, optic nerve)*
X	Jejunum*	X	Thymus		GLANDULAR
X	Ileum*			XX	Adrenal gland*+
X	Cecum*		UROGENITAL	X	Lacrimal/Harderian gland
X	Colon*	XX	Kidneys*+	X	Parathyroids*
X	Rectum*	X	Urinary bladder*	X	Thyroids*
XX	Liver*+	XX	Testes*+		OTHER
	Gall bladder* (not rat)	X	Epididymides*+	X	Bone (sternum and femur)
	Bile duct* (rat)	X	Prostate*	X	Skeletal muscle
X	Pancreas*	X	Seminal vesicle*	X	Skin*
		XX	Ovaries*+	X	Femur with joint
	RESPIRATORY	X	Uterus*+	X	Orbital gland
X	Trachea*	X	Mammary gland*	X	Zymbal's gland
X	Lung*++	X	Vagina	X	Muzzle
X	Nose*		Cervix	X	All gross lesions and masses*
X	Pharynx*				
X	Larynx*				

* Recommended for combined chronic toxicity/carcinogenicity studies based on Guideline 870.4300
\+ Organ weight required in combined chronic toxicity/carcinogenicity studies
++ Organ weight required if inhalation route

Organs and tissues were preserved in neutral buffered 4% formalin. Samples from animal #276 of the 600 ppm group were not processed due to advanced autolysis. All other animals of the control and 600 ppm groups were processed routinely, stained with hematoxylin and eosin, and examined microscopically. A peer review was performed that included all organs and tissues from 10% of the animals randomly selected from each dose group, target organs from all animals, and neoplastic lesions from all animals. A second peer review was performed on the treatment-related tumors (pancreatic tumors). The diagnoses reported in the tables were mutually agreed-on by the pathologists.

II. RESULTS

A. OBSERVATIONS

1. **Mortality:** As shown in table 2, no treatment-related effect was noted on mortality. In the carcinogenicity groups, the survival rates at study termination were 52-80%, without a dose-dependent effect of treatment.

TABLE 2. Number surviving to terminal necropsy in rats treated with terbutryn in the diet for up to 2 years. [a]					
	Dose (ppm)				
Week	0	30	100	300	600
Male	33 (66%)[a]	26 (52)	27 (54%)	39 (78%)	37 (74%)
Female	34 (68%)	27 (54%)	30 (60%)	35 (70%)	40 (80%)

a In Parentheses = % Survival

2. **Clinical signs of toxicity:** No treatment-related signs were noted in the animals (n=80).

B. **BODY WEIGHT AND BODY WEIGHT GAINS:** At 600 ppm, decreases ($p \leq 0.05$) in body weights were observed throughout treatment by 4-12% in the males and by 4-21% in the females (Table 3). Minor, transient decreases ($p \leq 0.05$) were also noted at 300 ppm in both sexes, but were not considered an adverse effect. During the first 14 weeks of treatment at 600 ppm, body weight gains decreased by 8% in males and by 18% in females. Overall body weight gain (Weeks 1-103) decreased ($p \leq 0.05$) by 15% in males and 29% in females at 600 ppm.

No effects of treatment were observed on body weights or body weight gains at 30 or 100 ppm.

C. **FOOD AND WATER CONSUMPTION, AND COMPOUND INTAKE**

1. **Food consumption:** At 600 ppm, food consumption was slightly decreased throughout the study, frequently attaining statistical significance, resulting in cumulative (Weeks 1-103) decreased food consumption (g/animal) of 5% in the males and 9% in the females. Additionally at 600 ppm, food consumption ratios (g food consumed/kg body weight/day) were increased from Week 22 (males) or 38 (females) throughout the remainder of the study, indicating food efficiency was impacted at this dose level. Maximum deviations from controls of 12% (males) and 16% (females) were obtained at Week 83.

No effects of treatment were observed on food consumption at 30, 100, or 300 ppm.

2. **Water consumption:** No treatment-related effect was observed on water consumption.

3. **Compound consumption:** The mean achieved dosages are reported in Table 1.

TABLE 3. Body weights and body weight gains (g) at selected intervals in rats treated with terbutryn in the diet for up to 2 years. [a]

Week	Dose (ppm)				
	0	30	100	300	600
Males					
1	227.7±15.7	225.1±15.7	226.6±16.8	222.3±15.8	220.7±17.1
2	285.5±18.8	282.4±22.1	284.5±21.3	276.6±18.7	274.8±19.5* (↓4)
14	480.6±44.4	474.9±55.4	479.2±53.9	459.8±42.2	453.0±47.8* (↓6)
26	558.8±53.9	550.1±71.6	553.6±68.8	531.0±53.4* (↓5)	519.5±61.6* (↓7)
87	764.6±100.3	753.9±106.5	745.4±125.9	718.3±78.9* (↓6)	688.2±86.0* (↓10)
99	751.7±127.3	739.0±102.9	723.7±99.5	705.2±84.0	664.4±88.7* (↓12)
103	737.5±145.9	720.0±109.7	705.6±77.4	700.5±89.3	653.8±90.4* (↓11)
BWG (1-14) [b]	252.9	249.8	252.6	237.5	232.3 (↓8)
BWG (14-54) [b]	197.7	197.4	192.2	182.6	153.9 (↓22)
BWG (54-79) [b]	78.8	83.2	68.5	76.8	74.3 (↓6)
BWG (79-103) [b]	-19.6	-35.5	-34.3	-18.7	-27.4 (↓40)
BWG (-1-103) [c]	545.9±141.5	532.2±104.8	515.2±75.9	510.3±88.0	464.7±85.2* (↓15)
Females					
1	169.5±13.0	171.3±13.3	168.8±14.1	172.6±11.2	166.3±11.3
2	197.7±15.7	200.1±15.5	197.1±14.7	198.6±13.4	189.4±13.4* (↓4)
14	295.7±33.4	297.4±25.0	292.7±25.1	292.1±25.5	269.6±17.1* (↓9)
46	367.2±60.1	364.1±43.3	361.2±46.4	346.7±38.6* (↓6)	311.2±24.1* (↓15)
74	426.2±78.5	437.6±69.8	417.6±77.4	401.5±76.9	338.1±35.0* (↓21)
103	435.5±80.1	447.6±78.0	460.7±84.3	427.8±90.3	352.4±45.2* (↓19)
BWG (1-14) [b]	126.2	126.1	123.9	119.5	103.3 (↓18)
BWG (14-54) [b]	86.8	85.9	84.7	68.2 (↓21)	48.8 (↓44)
BWG (54-79) [b]	50.3	61.0	54.7	44.0 (↓13)	26.0 (↓48)
BWG (79-103) [b]	2.7	3.3	28.6	23.5 (↑770)	8 (↑196)
BWG (-1-103) [c]	286.7±77.2	297.5±79.0	312.4±79.8	275.3±87.2	203.4±44.7* (↓29)

a Data (mean±SD, n=80 on Day 1) were obtained from Tables 8.7-8.8 on pages 98-118 and Table 8.10 on pages 129 and 138 of the study report. Percent difference from controls, calculated by reviewers, is included in parentheses.

b Body weight gains were calculated by the reviewers.

c The Sponsor reported cumulative body weight gain from Week -1 through Week 103. These values are reported in this table because standard deviation and statistic analyses were reported for these values.

* Significantly different ($p \leq 0.05$) from the control groups.

D. OPHTHALMOSCOPIC EXAMINATION: No treatment-related effects were observed during the ophthalmoscopic examinations.

E. BLOOD ANALYSES

1. **Hematology:** No adverse, treatment-related effects were observed on the measured hematology parameters. All differences ($p \leq 0.05$) in the treated groups compared to controls were considered minor, transient, and/or unrelated to dose.

2. **Clinical chemistry:** No adverse, treatment-related effects were observed on the measured clinical chemistry parameters. In the 600 ppm females, increased levels of serum inorganic phosphorus were observed throughout treatment (↑19-61%). These increases were significant ($p \leq 0.05$) during Weeks 27-105, and exceeded the 90% confidence limits of the

historical controls during Weeks 13-78. However, in the absence of corroborating evidence of toxicity, these increases were not considered adverse. All other differences ($p \leq 0.05$) in the treated groups compared to controls were considered minor, transient, and/or unrelated to dose.

F. URINALYSIS: No treatment-related effects were observed during urinalysis.

G. SACRIFICE AND PATHOLOGY

1. **Organ weights:** No treatment-related effects were observed on organ weights. Differences ($p \leq 0.05$) were minor, within the 90% confidence limits of the historical controls, and/or were not corroborated by other pathological findings.

2. **Gross pathology:** After 1 year, no treatment-related effects were noted on the incidence of macroscopic lesions.

   After 2 years, an increased incidence in pancreatic nodules was observed in the males at 300 ppm (13 affected/70 examined) and 600 ppm (16/70) compared to the controls (7/70; Table 4). Pancreas nodules were not observed at the interim sacrifice, and a dose-related effect was not observed in females. These nodules corresponded mainly to acinar cell adenomas microscopically.

TABLE 4. Pancreas nodules in male rats (# rats affected/# examined [%]) treated with terbutryn in the diet after up to 2 years of administration. [a]

Dose (ppm)				
0	30	100	300	600
7/70 (10)	10/70 (14)	8/70 (11)	13/70 (19)	16/70 (23)

a Data were obtained from page 57 of the study report.

3. **Microscopic pathology**

a. **Non-neoplastic:** After 1 year, no treatment-related effects were noted on the incidence of microscopic lesions.

   After 2 years, treatment-related increased ($p \leq 0.05$; except as noted) incidences were noted for the following: (% affected in treated [severity] vs controls [severity]; Table 5) at 600 ppm: (i) lung foam cells in the males (68% [minimal to massive] vs 44% [minimal to massive]); (ii) thyroid gland follicular cell hypertrophy in males (60% [minimal to slight] vs 34% [minimal to slight]); (iii) thyroid gland follicular cell hyperplasia in males (10% [moderate to marked] vs 2% [massive]); (iv) spleen hemosiderosis in females (54% [minimal to marked] vs 28% [minimal to moderate]); (v) uterus hyperplastic glandular cyst (16% [minimal to marked] vs 10% [minimal to moderate]; NS); and (vi) uterus stromal polyp (12% [moderate to marked] vs 2% [moderate]). The number of animals with findings

of moderate severity or greater was also increased at 600 ppm, excluding follicular hypertrophy. All these incidences and severity supported these are treatment-related effects.

TABLE 5. Selected microscopic findings in rats (# rats affected/# examined [%]) treated with terbutryn in the diet for up to 2 years.[a]

Finding	Dose (ppm) 0	30	100	300	600
Males					
Lung Foam cell (Total)	22/50 (44)	22/50 (44)	27/50 (54)	23/49 (47)	34/50* (68)
Minimal	10	9	15	14	13
Slight	6	5	6	4	6
Moderate	2	6	3	4	8
Marked	3	2	3	1	6
Massive	1	---	---	---	1
Thyroid gland Follicular cell hypertrophy (Total)	17/50 (34)	18/48 (38)	15/46 (33)	18/48 (38)	30/50* (60)
Minimal	10	14	8	11	20
Slight	7	4	7	6	10
Moderate	---	---	---	1	---
Follicular cell hyperplasia (Total)	1/50 (2)	1/48 (2)	2/46 (4)	4/48 (8)	5/50* (10)
Minimal	---	---	---	1	---
Slight	---	---	1	1	---
Moderate	---	---	1	2	2
Marked	---	1	---	---	3
Massive	1	---	---	---	---
Females					
Spleen Hemosiderosis (Total)	14/50 (28)	16/50 (32)	16/50 (32)	15/49 (31)	27/50* (54)
Minimal	7	11	6	9	5
Slight	5	2	5	5	13
Moderate	2	1	3	---	8
Marked	---	2	2	1	1
Uterus Hyperplastic glandular cyst (Total)	5/50 (10)	7/50 (14)	4/50 (8)	7/50 (14)	8/50 (16)
Minimal	3	3	3	3	2
Slight	1	1		3	5
Moderate	1	3	1	1	---
Marked	---	---	---	---	1
Polyp, stromal (Total)	1/50 (2)	3/50 (6)	2/50 (4)	4/50 (8)	6/50* (14)
Minimal	---	---	---	1	---
Slight	---	1	1	1	---
Moderate	1	2	1	---	3
Marked	---	---	---	1	3
Massive	---	---	---	1	---

a Data were obtained from pages 1166-2308 in the study report.
* Significantly different ($p \leq 0.05$) from the control groups

b. **Neoplastic:** After 1 year, no treatment-related effects were noted on the incidence of neoplastic lesions.

After 2 years, dose responsive incidence of pancreatic acinar adenoma was increased (Table 6): one tumor (47% treated vs. 21% controls; $p \leq 0.05$), two tumors (20% treated vs. 2% controls), and more than two tumors (8% treated vs. 0%; Table 6). The incidence is higher than the historical incidence of proliferative lesions in the exocrine pancreases of untreated male rats (Table 7).

The incidence of adenocarcinoma was unaffected by treatment. No effect was observed on neoplastic incidence in the pancreas of females. The incidences of other neoplastic lesions were similar to controls. Neoplastic summary data are provided in Attachment 1 of this DER.

TABLE 6. Pancreatic acinar neoplasia in male rats (# rats affected/# examined [%]) treated with terbutryn in the diet after up to 2 years of administration. [a]

Finding	Dose (ppm)				
	0	30	100	300	600
Adenoma (first)	10/47 (21)	7/46 (15)	17/45 (38)	12/48 (25)	23/49* (47)
Adenoma (second)	1	1	3	5	10
Adenoma (multiple)	0	0	0	1	4
Adenocarcinoma	1	2	1	0	1

a Data were obtained from page 1106 and 2336 of the study report.
* Significantly different ($p \leq 0.05$) from the control groups

III. DISCUSSION and CONCLUSIONS

No adverse, treatment-related effects were observed on mortality, clinical signs, water consumption, ophthalmoscopic examinations, hematology, clinical chemistry, urinalysis, or organ weights.

Systemic toxicity was observed at 600 ppm. Body weights were decreased ($p \leq 0.05$) throughout treatment by 4-12% in the males and by 4-21% in the females. During the first 14 weeks of treatment, body weight gains decreased by 8% in males and by 18% in females. Overall body weight gains (Weeks 1-103) decreased ($p \leq 0.05$) by 15% in males and 29% in females. Food consumption was slightly decreased throughout the study, frequently attaining statistical significance, resulting in cumulative (Weeks 1-103) decreased food consumption (g/animal) of 5% in the males and 9% in the females. Additionally, food consumption ratios (g food consumed/kg body weight/day) were increased from Week 22 (males) or 38 (females) throughout the remainder of the study, indicating food efficiency was impacted at this dose level. Maximum deviations from controls of 12% (males) and 16% (females) were obtained at Week 83.

TABLE 7. Historical Control data of proliferative lesions in the exocrine pancreases of untreated male rats. [a]

Study No.	Date of First Dose	Adenoma Acinar 1st (b)	Adenoma Acinar 2nd (c)	Adenoma Acinar Mul (d)	Organ Examined
921064	06/92	1	0	0	50
911123	08/92	2	1	0	50
926007	08/92	4	1	0	57
922816	05/93	1	0	0	50
923178	05/93	3	1	0	49
923151	06/93	1	0	0	49
936141	01/94	3	0	0	75
936141	01/94	4	0	0	75
943038	10/94	2	1	0	49
942110	08/95	7	1	0	49
951029	02/96	5	2	1	49
Total		33	7	1	602
Rel. Incidence (e)		5.48%	1.16%	0.17%	
SD (f)		3.81%	1.36%	0.62%	
Range High (#/organ examine%)		7/49 (14.29%)	2/49 (4.08%)	1/49 (2.04%)	
Range Low (#/organ examine%)		1/50 (2.00%)	0/75 (0.00%)	0/75 (0.00%)	

a Data were obtained from page 62 of the study report, data collected from Stein Syngenta Corp Protection, AG, Sten, Switzerland.
b. Animals with acinar Adenoma 1st (adenoma of exocrine pancreases)
c. Animals with acinar Adenoma 2nd (adenoma of exocrine pancreases)
d. Animals with acinar Adenoma mul (adenoma of exocrine pancreases)
e. Relative Incidence = # of incidences / total number of organ examined.
f. Standard deviation of relative incidence.

After 2 years, treatment-related increased ($p \leq 0.05$) incidences were noted in the thyroid follicular cells (% affected in treated [severity] vs controls [severity]) at 600 ppm: hypertrophy in males (60% [minimal to slight] vs 34% [minimal to slight]); and hyperplasia in males (10% [moderate to marked] vs 2% [massive]). These are considered as treatment related effects. Significant thyroid tumor incidents were reported in the 1980 rat oral chronic/cancer study (MRID 00035923).

In addition, at 600ppm, there were treatment-related, increased incidences of pulmonary alveolar foam cells, splenic hemosiderosis, stromal polyps in the uterus, and glandular cystic hyperplasia of the endometrium. All these incidences are considered treatment-related effects. Slightly increased levels of phosphorous were observed throughout treatment (↑19-61%). These increases were significant ($p \leq 0.05$) during Weeks 27-105, and exceeded the 90% confidence limits of the historical controls during Weeks 13-78. In the absence of corroborating evidence of toxicity, these increases were not considered adverse.

The LOAEL is 600 ppm (equivalent to 24.8/29.8 mg/kg/day in males/females), based on decreased body weights, body weight gains, food consumption and microscopic lesions in both sexes. The NOAEL is 300 ppm (equivalent to 12.0/14.0 mg/kg/day in males/females).

After 2 years at 600 ppm in male rats, the incidence of pancreatic acinar adenoma was increased: one tumor (47% treated vs 21% controls; $p \leq 0.05$), two tumors (20% treated vs 2% controls), and more than two tumors (8% treated vs. 0%). Dosing was considered adequate based on decreased body weights and body weight gains. Because (i) the effect did not show a clear dose-dependency manner; (ii) the effect was seen in male rats only; and (iii) the control group has incidence (21%) higher than the historical control incidences (ranging from 2 to 14.29%), reviewer agree the researcher's discussion, the toxicological significance of the increased pancreatic acinar adenoma is questionable.

There are two previous cancer studies:

Mouse two year cancer/chronic study (MRID 00029135):

A two year carcinogenicity study in Charles River CD-1 mice (MRID # 00029153) is available, in which technical terbutryn was administered in the diet at levels of 0, 3, 1000 and 3000 ppm. The test material was terbutryn technical. No treatment related effects were seen on general behavior, appearance, body weight gain, food consumption or survival. No evidence of oncogenicity was observed for terbutryn in this study.

Rat two-year cancer/chronic study (MRID 00035923)

In the rat two year cancer/chronic study, CD rats (MRID # 00035923) is available in which the oncogenic potential of technical terbutryn was studies. Levels tested were 0, 2, 300 and 3000 ppm (0, 0.1, 15, and 150 mg/kg/day). At 3000 ppm in the diet terbutryn induced a statistically significant increase in the number of mammary tumor bearing female rats, in combined hepatocellular adenomas and carcinomas in female rats in

combined thyroid follicular cell adenomas and carcinomas in male rats and in testicular interstitial cell adenomas in males at the highest dose tested.

On the December 23, 1987, Agency presented the study results of the two previous chronic/cancer studies to the Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP). SAP concluded "tumors were induced at multiple sits only at the highest dose, which exceeded a maximum tolerated dose (MTD). Good dose-response data were not available due to the large spread between doses. Therefore the panel believes that an interim category C is appropriate, but that this could be reduced to a category D if negative data from more appropriate does were submitted. Furthermore, the panel does not believe a quantitative risk assessment (for the carcinogenic effects) is justified since positive tumor Data occurred only at does that exceeded the MTD".

On January 13, 1988, the Office of Pesticide Programs (OPP) Peer review Committee for Terbutryn meet to discuss the carcinogenic concern of terbutryn based on the SAP's recommendation. It concluded "the committee concurred with the SAP decision, but felt that science Terbutryn was classified as interim C and science the dosage levels for the rat study (MRID 00035923) were poorly chosen, that another rat oncogenicity study should be required with particular attention paid to dose selection".

Although incidences of hypertrophy of thyroid follicular cells were noticed in current study, it only happened at highest level tested (600 ppm), and no thyroid follicle cell adenoma was noticed. No mammary tumor, no hepatocellular adenomas and/or carcinomas, and testicular interstitial cell adenomas were noticed in the study. Therefore, based on the current study results will not change Agency's classification on interim group C carcinogen and quantitative risk assessment for the carcinogenetic potential of Terbutryn is not needed.

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.4300; OECD 453) for a combined chronic toxicity/carcinogenicity study in rats.

C. **STUDY DEFICIENCIES:** The following minor deficiencies were noted:

- The heart, epididymides, and uterus were not weighed.
- Tabulated severity data were not provided for histological lesions.
- The summary incidence reported at 600 ppm 9/50 females with uterine hyperplastic glandular cysts and 7/50 uterine stromal polyps; however, the reviewers only found 8/50 and 6/50, respectively, from the individual data.

ATTACHMENT

The following pages are copies of pages 1104-1108 and 1109-1112 in the study report.

PATHOLOGY REPORT PAGE : 1104
SUMMARY TABLES P951040

TEST ARTICLE : GS 14260 tech. *PATHOL. NO.*: 10043 ABR
TEST SYSTEM : RAT, 24-MONTH, ORAL *DATE* : 22-DEC-99
SPONSOR : Crop Protection Division *PathData® System V5.1b*

NUMBER OF ANIMALS WITH NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. DEATHS

SEX :						MALE
DOSE GROUP:	1	2	3	4	5	
NO.ANIMALS:	50	50	50	50	50	
ADRENAL GLANDS :	50	49	49	48	50	
- ADENOMA CORTICAL :	3	6	5	3	4	
- MYELOLIPOMA :	-	1	-	-	-	
- metastat. sarcoma :	-	1	-	-	-	
ADRENAL MEDULLAS :	50	49	49	48	50	
- TUMOR MEDULLARY BEN.:	2	-	4	7	3	
- TUMOR MEDULLARY MAL.:	2	1	-	1	-	
BONE :	-	2	-	2	-	
- OSTEOSARCOMA :	-	1	-	-	-	
BONE MARROW :	50	50	50	49	50	
- HEMANGIOMA :	-	1	-	-	-	
BRAIN :	50	50	50	49	50	
- ASTROCYTOMA MALIGN. :	1	1	-	-	-	
- OLIGODENDROGLI. BEN.:	1	-	-	-	-	
- OLIGODENDROGLI. MAL.:	-	2	-	-	-	
- TUM.GRANULAR CE.BEN.:	-	-	2	-	-	
- metastat. tumor :	1	2	-	-	-	
EPIDIDYMIDES :	50	50	50	49	50	
- MESOTHELIOMA BENIGN :	-	-	1	-	-	
EYES :	50	50	46	49	50	
- metastat. carcinoma :	-	-	-	-	1	
- metastat. sarcoma :	1	-	-	-	-	
HEART :	50	50	50	49	50	
- SCHWANNOMA ENDOC.BEN:	-	1	-	1	1	
- SCHWANNOMA ENDOC.MAL:	-	-	-	-	1	
KIDNEYS :	50	49	50	49	50	
- LIPOSARCOMA RENAL :	-	-	1	-	-	
- metastat. sarcoma :	-	1	-	-	-	

PATHOLOGY REPORT PAGE : 1105
SUMMARY TABLES P951040

TEST ARTICLE : GS 14260 tech. *PATHOL. NO.* : 10043 ABR
TEST SYSTEM : RAT, 24-MONTH, ORAL *DATE* : 22-DEC-99
SPONSOR : Crop Protection Division *PathData® System V5.1b*

NUMBER OF ANIMALS WITH NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STAIUS AT NECROPSY: K0, INCL. DEAIHS

SEX :						MALE
DOSE GROUP:	1	2	3	4	5	
NO.ANIMALS:	50	50	50	50	50	
LIVER :	50	50	50	49	50	
- ADENOMA HEPATOCE.1st:	3	1	-	1	3	
- ADENOMA HEPATOCE.2nd:	2	1	-	-	2	
- ADENOMA HEPATOCE.mul:	1	1	-	-	2	
- CHOLANGIOCARCINOMA :	1	-	-	-	-	
- metastat. carcinoma :	-	1	-	-	1	
- metastat. sarcoma :	-	1	-	-	-	
LUNG :	50	50	50	49	50	
- CARCINOMA BROALV. :	-	1	1	-	1	
- metastat. carcinoma :	-	-	-	1	-	
- metastat. sarcoma :	-	1	-	-	-	
LYMPH NODE :	8	1	2	4	3	
- metastat. carcinoma :	-	-	1	-	-	
MAMMARY GLAND :	50	50	49	47	50	
- ADENOCARC.IN FIBROAD:	-	1	-	-	-	
- ADENOCARCINOMA 1st :	-	1	-	-	-	
- FIBROADENOMA 1st :	1	1	-	1	-	
MESENT. LYMPH NODE :	50	49	49	48	49	
- HEMANGIOMA :	2	-	2	-	-	
NASOPHARYNX :	-	-	-	-	1	
- CARCINOMA SQUAMOUS :	-	-	-	-	1	
ORAL CAVIIY :	-	1	2	-	1	
- CARCINOMA SQUAMOUS :	-	-	-	-	1	

PATHOLOGY REPORT PAGE : 1106
SUMMARY TABLES P951040

TEST ARTICLE : GS 14260 tech. *PATHOL. NO.* : 10043 ABR
TEST SYSTEM : RAT, 24-MONTH, ORAL *DATE* : 22-DEC-99
SPONSOR : Crop Protection Division *PathData® System V5.1b*

NUMBER OF ANIMALS WITH NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. DEATHS

SEX :						MALE
DOSE GROUP:	1	2	3	4	5	
NO ANIMALS:	50	50	50	50	50	
PANCREAS :	47	46	45	48	49	
- ADENOCARC.ACINAR :	1	2	1	-	1	
- ADENOMA ACINAR 1st :	10	7	17	12	23	
- ADENOMA ACINAR 2nd :	1	1	3	5	10	
- ADENOMA ACINAR mul :	-	-	-	1	4	
- IUM. ISLET CELL MAL.:	-	1	-	1	2	
- TUM.ISL.CELL BEN.1st:	9	4	7	3	3	
- TUM.ISL.CELL BEN 2nd:	-	-	1	2	-	
- metastat. sarcoma :	-	1	-	-	-	
PARATHYROID GLAND :	50	49	45	49	49	
- ADENOMA :	-	-	1	-	-	
PERIOCULAR TISSUES :	2	-	-	1	-	
- FIBROSARCOMA :	1	-	-	-	-	
- SCHWANNOMA MALIGNANT:	1	-	-	-	-	
PITUITARY GLAND :	50	50	50	49	49	
- ADENOCARC. P. DIST. :	-	2	-	-	1	
- ADENOCARC.P.INTERMED:	-	-	1	-	-	
- ADENOMA P. DISTALIS :	22	19	23	20	16	
- ADENOMA P. INTERMED.:	2	-	-	-	-	
PROSTATE GLAND :	49	50	50	47	50	
- ADENOCARCINOMA :	-	1	-	-	-	
- ADENOMA 1st :	10	13	8	12	12	
- ADENOMA 2nd :	6	7	5	6	2	
- ADENOMA mul. :	1	4	2	2	2	

PATHOLOGY REPORT PAGE : 1107
SUMMARY TABLES P951040

TEST ARTICLE : GS 14260 tech. *PATHOL. NO.*: 10043 ABR
TEST SYSTEM : RAI, 24-MONIH, ORAL *DATE* : 22-DEC-99
SPONSOR : Crop Protection Division *PathData® System V5.1b*

NUMBER OF ANIMALS WITH NEOPLASIIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

SEX :						MALE
DOSE GROUP:	1	2	3	4	5	
NO.ANIMALS:	50	50	50	50	50	
SKIN/SUBCUTIS :	50	50	50	49	50	
- CARCINOMA BASAL CELL:	-	-	1	1	-	
- FIBROMA 1st :	9	9	8	9	8	
- FIBROMA 2nd :	-	2	2	-	-	
- FIBROMA mul :	-	1	1	-	-	
- FIBROSARCOMA :	3	2	1	-	-	
- HEMANGIOSARCOMA :	1	-	-	-	-	
- KERATOACANTHOMA 1st :	-	4	2	1	2	
- KERATOACANTHOMA 2nd :	-	-	-	-	1	
- LIPOMA :	1	2	1	2	-	
- LIPOSARCOMA :	-	-	1	-	-	
- SARCOMA NOS :	2	-	2	1	-	
- SCHWANNOMA MALIGNANI:	1	-	-	-	-	
- TUM.BASAL CELL BEN. :	-	-	-	2	-	
- TUM.HAIR FOLLIC. BEN:	1	1	-	-	-	
- metastat. sarcoma :	1	-	-	-	-	
SMALL INIESTINE :	46	45	45	47	49	
- ADENOCARCINOMA :	1	-	-	-	2	
SPLEEN :	49	50	50	49	50	
- HEMANGIOMA :	1	-	-	-	-	
SYSTEMIC NEOPLASIAS :	2	2	1	2	-	
- LEUKEMIA MYELOID :	-	2	-	1	-	
- LYMPHOMA MALIGNANT :	2	-	1	1	-	
TESTES :	50	50	50	49	50	
- TUM.LEYDIG C.BEN 1st:	3	2	4	2	2	
- TUM.LEYDIG C.BEN 2nd:	1	1	-	-	-	
- TUM.LEYDIG C.BEN mul:	1	-	-	-	-	

PATHOLOGY REPORT PAGE : 1108
SUMMARY TABLES P951040

TEST ARTICLE : GS 14260 tech. *PATHOL. NO.*: 10043 ABR
TEST SYSTEM : RAT, 24-MONTH, ORAL *DATE* : 22-DEC-99
SPONSOR : Crop Protection Division *PathData® System V5.1b*

NUMBER OF ANIMALS WITH NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. DEATHS

SEX :						MALE
DOSE GROUP:	1	2	3	4	5	
NO ANIMALS:	50	50	50	50	50	
THYROID GLAND :	50	48	46	48	50	
- ADENOCARC. FOLLICULAR:	-	-	2	-	-	
- ADENOMA FOLLICULAR :	2	1	1	4	3	
- TUMOR C-CELL BEN. 1st:	4	5	4	9	4	
- TUMOR C-CELL BEN. 2nd:	1	-	-	2	-	
- TUMOR C-CELL MALIGN. :	-	1	1	1	-	
ZYMBAL'S GLANDS :	49	46	45	48	50	
- CARCINOMA SQUAMOUS :	-	-	-	-	1	

PATHOLOGY REPORT PAGE : 1109
SUMMARY TABLES P951040

TEST ARTICLE : GS 14260 tech. *PATHOL. NO.* : 10043 ABR
TEST SYSTEM : RAI, 24-MONTH, ORAL *DATE* : 22-DEC-99
SPONSOR : Crop Protection Division *PathData® System V5.1b*

NUMBER OF ANIMALS WITH NEOPLASIIC LESIONS BY ORGAN/GROUP/SEX
STAIUS AT NECROPSY: K0, INCL. DEAIHS

SEX :						FEMALE
DOSE GROUP:	1	2	3	4	5	
NO.ANIMALS:	50	50	50	50	50	
ABDOMINAL CAVITY :	-	-	2	2	1	
- SARCOMA NOS :	-	-	1	-	1	
- metastat. carcinoma :	-	-	1	-	-	
- metastat. tumor :	-	-	-	1	-	
ADRENAL GLANDS :	50	50	50	50	50	
- ADENOMA CORTICAL :	1	2	1	-	1	
- metastat. carcinoma :	-	-	1	-	-	
ADRENAL MEDULLAS :	50	49	50	50	50	
- IUMOR MEDULLARY BEN. :	1	1	-	-	-	
- IUMOR MEDULLARY MAL. :	-	-	-	1	-	
AXILLARY LYMPH NODE :	49	50	49	49	49	
- metastat. carcinoma :	1	-	1	-	-	
BONE :	1	1	1	1	-	
- OSTEOMA :	-	-	-	1	-	
- OSTEOSARCOMA :	-	-	1	-	-	
BRAIN :	50	50	50	49	50	
- ASTROCYTOMA MALIGN. :	-	2	-	1	1	
- IUM.GRANULAR CE.BEN. :	-	-	-	1	-	
CLITORAL GLAND :	1	-	-	-	-	
- ADENOCARCINOMA :	1	-	-	-	-	
EYES :	50	50	50	49	50	
- metastat. sarcoma :	-	-	-	-	1	
HEART :	50	50	49	50	50	
- SCHWANNOMA ENDOC.BEN:	-	-	1	-	-	
- SCHWANNOMA ENDOC.MAL:	-	-	-	1	1	
- metastat. carcinoma :	-	-	1	-	-	

PATHOLOGY REPORT PAGE : 1110
SUMMARY TABLES P951040

TEST ARTICLE : GS 14260 tech. *PATHOL. NO.* : 10043 ABR
TEST SYSTEM : RAT, 24-MONIH, ORAL *DATE* : 22-DEC-99
SPONSOR : Crop Protection Division *PathData® System V5.1b*

NUMBER OF ANIMALS WITH NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

SEX :						FEMALE
DOSE GROUP:	1	2	3	4	5	
NO ANIMALS:	50	50	50	50	50	
KIDNEYS :	50	50	50	50	50	
- metastat. carcinoma :	-	-	1	-	-	
- metastat. sarcoma :	-	1	-	-	-	
LARGE INTESTINE :	48	49	49	46	49	
- metastat. sarcoma :	1	-	-	-	-	
LIVER :	50	50	50	50	50	
- metastat. sarcoma :	-	-	-	-	1	
LUNG :	50	50	50	50	50	
- metastat. carcinoma :	-	-	3	-	1	
- metastat. sarcoma :	1	1	-	-	1	
- metastat tumor :	-	-	-	2	-	
MAMMARY GLAND :	50	50	50	50	50	
- ADENOCARC. IN FIBROAD:	-	1	-	-	-	
- ADENOCARCINOMA 1st :	9	4	4	1	6	
- ADENOCARCINOMA 2nd :	1	1	1	-	1	
- ADENOMA 1st :	4	1	1	-	1	
- FIBROADENOMA 1st :	28	26	31	26	13	
- FIBROADENOMA 2nd :	11	12	11	7	3	
- FIBROADENOMA mul :	2	5	4	1	1	
MESENT. LYMPH NODE :	50	50	50	49	50	
- HEMANGIOMA :	1	2	2	-	-	
NASAL CAVITIES :	1	-	1	1	1	
- CHONDROMA :	-	-	-	-	1	
OVARIES :	50	50	50	50	50	
- CYSTADENOMA :	3	3	4	3	2	
- TUM. GRANULOSA BEN. :	-	-	-	1	1	
- TUM SERTOLI BENIGN :	1	1	1	1	-	
- TUM. SERTOLI MALIGNAI:	-	-	-	1	-	
- TUM. SEX CORD BENIGN :	2	2	4	2	1	
- metastat. carcinoma :	-	-	1	-	-	

PATHOLOGY REPORT PAGE : 1111
SUMMARY TABLES P951040

TEST ARTICLE : GS 14260 tech *PATHOL. NO.*: 10043 ABR
TEST SYSTEM : RAT, 24-MONTH, ORAL *DATE* : 22-DEC-99
SPONSOR : Crop Protection Division *PathData® System V5.1b*

NUMBER OF ANIMALS WITH NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. DEATHS

SEX :						FEMALE
DOSE GROUP:	1	2	3	4	5	
NO. ANIMALS:	50	50	50	50	50	
PANCREAS :	50	50	50	48	50	
- TUM.ISL.CELL BEN.1st:	3	3	2	2	1	
- TUM.ISL.CELL BEN.2nd:	-	-	1	-	-	
- metastat. sarcoma :	1	-	-	-	-	
PERIOCULAR TISSUES :	1	-	-	-	1	
- metastat sarcoma :	-	-	-	-	1	
PITUITARY GLAND :	50	49	50	49	50	
- ADENOCARC. P DIST. :	1	-	-	1	-	
- ADENOMA P. DISTALIS :	13	20	19	12	18	
SALIVARY GLANDS :	50	50	48	49	49	
- TUMOR MIXED MALIGN. :	-	-	-	1	-	
- metastat. sarcoma :	-	-	-	-	1	
SKELETAL MUSCLE :	50	50	50	50	50	
- metastat. sarcoma :	1	-	-	-	1	
SKIN/SUBCUTIS :	50	50	50	50	50	
- CARCINOMA BASAL CELL:	-	-	1	-	-	
- FIBROMA 1st :	1	4	-	3	1	
- FIBROSARCOMA :	1	-	1	-	-	
- LIPOMA :	-	1	-	-	-	
- PAPILLOMA SQUAMOUS :	1	-	-	-	-	
- TUM.UNCLASSIF.MALIG. :	-	-	1	-	-	
- metastat carcinoma :	-	-	1	-	-	
- metastat. sarcoma :	-	-	-	-	1	
SMALL INTESTINE :	48	48	46	45	49	
- LEIOMYOSARCOMA :	-	-	-	-	1	
SPLEEN :	50	50	50	49	50	
- SARCOMA NOS :	1	-	-	-	-	
STOMACH :	49	49	50	49	50	
- metastat. sarcoma :	1	-	-	-	-	

PATHOLOGY REPORT PAGE : 1112
SUMMARY TABLES P951040

TEST ARTICLE : GS 14260 tech. *PATHOL. NO.*: 10043 ABR
TEST SYSTEM : RAT, 24-MONIH, ORAL *DATE* : 22-DEC-99
SPONSOR : Crop Protection Division *PathData® System V5.1b*

NUMBER OF ANIMALS WITH NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STAIUS AT NECROPSY: K0, INCL. DEATHS

SEX :						FEMALE
DOSE GROUP:	1	2	3	4	5	
NO ANIMALS:	50	50	50	50	50	
SYSIEMIC NEOPLASIAS :	-	-	-	-	1	
- LYMPHOMA MALIGNANT :	-	-	-	-	1	
- SARCOMA HISTIOCYTIC :	-	-	-	-	1	
IHYROID GLAND :	50	50	49	49	50	
- ADENOCARC. FOLLICULAR:	-	-	-	-	1	
- ADENOMA FOLLICULAR :	1	-	-	-	1	
- TUMOR C-CELL BEN. 1st:	5	6	-	5	-	
- TUMOR C-CELL BEN. 2nd:	2	-	-	-	-	
- TUMOR C-CELL MALIGN.:	-	-	-	2	-	
- metastat. sarcoma :	-	-	-	-	1	
TONGUE :	50	50	50	49	50	
- PAPILLOMA SQUAMOUS :	1	-	-	-	-	
URINARY BLADDER :	50	49	49	46	50	
- CARCINOMA TRANSIT. :	-	-	1	-	-	
UTERUS :	50	50	50	50	50	
- ADENOMA :	1	1	-	-	2	
- metastat. sarcoma :	-	1	-	-	-	
VAGINA :	50	49	50	49	50	
- LEIOMYOSARCOMA :	-	1	-	-	-	
- SCHWANNOMA MALIGNANT:	-	-	1	-	-	
ZYMBAL'S GLANDS :	50	48	47	49	45	
- CARCINOMA SQUAMOUS :	-	-	1	-	-	
- metastat sarcoma :	-	-	-	-	1	